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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/660,794	09/12/2003	Matthias Gerlach	029310.52760US	9303
23911	7590	03/02/2005	EXAMINER	
CROWELL & MORING LLP INTELLECTUAL PROPERTY GROUP P.O. BOX 14300 WASHINGTON, DC 20044-4300			MCKENZIE, THOMAS C	
			ART UNIT	PAPER NUMBER
			1624	

DATE MAILED: 03/02/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

JLC

Office Action Summary

Application No.

10/660,794

Applicant(s)

GERLACH ET AL.

Examiner

Thomas McKenzie, Ph.D.

Art Unit

1624

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 12 September 2003.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-40 is/are pending in the application.
- 4a) Of the above claim(s) _____ is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-7 and 9-40 is/are rejected.
- 7) ☒ Claim(s) 8 is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☒ All b) ☐ Some * c) ☐ None of:
1. ☒ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).
- * See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)
Paper No(s)/Mail Date 3/5/04.
- 4) ☐ Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____.
- 5) ☐ Notice of Informal Patent Application (PTO-152)
- 6) ☐ Other: _____.

DETAILED ACTION

1. This action is in response to an application filed on 9/12/03. There are forty claims pending and forty under consideration. Claims 1-8 and 19 are compound claims. Claim 20-23 are 40 are composition claims. Claims 24-41 are method of using claims. Claims 9-18 are method of making claims. This is the first action on the merits. The application concerns some hetero fused pyrimidine compounds, compositions, and uses thereof.

Abstract

2. Applicant is reminded of the proper content of an abstract of the disclosure. A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. In chemical patent abstracts for compounds or compositions, the general nature of the compound or composition should be given as well as its use, *e.g.*, "The compounds are of the class of alkyl benzene sulfonyl ureas, useful as oral anti-diabetics." The abstract is too short and generic. Examiner suggests claim 1, lines 1-7, including the figure, and the utility.

Claim Rejections - 35 USC § 112

3. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 20-23 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claim limitation "a medicament" is unclear for it is uncertain if these are compound or composition claims. If they are composition claims then they are also rejected as being incomplete for omitting essential elements, such omission amounting to a gap between the elements. See MPEP § 2172.01. The omitted elements are: the carrier needed to make the composition. If claims 20-23 are compound claim then objection is made to them under 37 CFR 1.75 as being a substantial duplicates of claims 1-4. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

4. If claim 20 is a composition claim then objection is made to claim 42 under 37 CFR 1.75 as being a substantial duplicate of claim 20. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k).

5. Claims 36-39 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The specification does not set forth any steps involved in determining how to identify “a medical condition or illness affected by modulating nucleoside transport proteins, adenosine kinase, adenosine deaminase, or A1, A2, or A3 receptors”. It is unclear what diseases and treatments applicant is intending to encompass. Determining whether a given disease responds or does not respond to such a receptor antagonist and thus, covered by the claim language, will require extensive and potentially inconclusive clinical research. Without such clinical research to identify the patients and diseases Applicants intend to treat, the physician skilled in the clinical arts cannot determine the metes and bounds of the claim. Hence, the claims are indefinite.

6. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 28-31 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Alzheimer's disease, does not reasonably provide enablement for treating any of the other claimed diseases. The specification does not enable any physician skilled in the art of medicine, to make

the invention commensurate in scope with these claims. The how to make requirement of the enablement statute, when applied to process claims, refers to operability and how to make the claimed process work. "The factors to be considered [in making an enablement rejection] have been summarized as the quantity of experimentation necessary, the amount of direction or guidance presented, the presence or absence of working examples, the nature of the invention, the state of the prior art, the relative skill of those in that art, the predictability or unpredictability of the art and the breadth of the claims", *In re Rainer*, 146 USPQ 218 (1965); *In re Colianni*, 195 USPQ 150, *Ex parte Formal*, 230 USPQ 546. The four main issues are the lack of any correlation between clinical efficacy for disease treatment and Applicants' three *in vitro* assays, the narrow scope of the compounds tested in these assays, the state of the prior art, and the breadth of the claims.

There is an *in vitro* assay, drawn to binding to the ionotropic NMDA receptor, described in the passage spanning line 25, page 71 to line 19, page 73 with data for only five of Applicants' compounds. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to clinical efficacy for the treatment of any diseases. Applicants state these five compounds are antagonists at this receptor. However, it is not apparent to the Examiner how this was

determined since only binding data was obtained. Binding data alone will not distinguish between an agonist and an antagonist at a receptor site.

There is an *in vitro* assay, drawn to inhibition of nucleoside transport protein, described in the passage spanning line 21, page 73 to line 13, page 74 with data for ten of Applicants' compounds. These ten compounds are all different than the five compounds active at the NMDA receptor. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to clinical efficacy for the treatment of any diseases.

There is an *in vitro* assay, drawn to binding to the purine A₃ receptor, described in the passage spanning line 14, page 74 to line 2, page 75 with data for just a single compound of Applicants'. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to clinical efficacy for the treatment of any diseases. Applicants do not state and it is not apparent to the Examiner if this one compounds is an agonist or an antagonist at this receptor. This lone compound is different than the fifteen compounds discussed above. Applicants do not state and it is not recognized in the clinical arts this assay is correlated to clinical efficacy for the treatment of any diseases. The state of the clinical arts in therapy of Alzheimer's disease is that the NMDA receptor antagonist Memantine was approved in Europe for such use in 2002. This

evidence is found in paragraph 3, page S47 and paragraph four, page S48 of Mobius (Int J Geriatr Psychiatry.). The state of the clinical arts in therapy of stroke that the NMDA receptor antagonists CNS 5161 and GV 150526 had not shown clinical efficacy for such use in 2001 or 2002. This evidence is found in the abstract of Lees (Cerebrovas. Dis.) and paragraph two, page 306 and paragraphs five-six, page 311 of Walters (Br J Clin Pharmacol.). Thus, the present claims to treatment of cerebral ischemias and cerebral oedemas lack the required nexus to the assay data in the specification. AdditionLY, Low (Int J Clin Pharmacol Ther.) states in his abstract that neurotoxicity is a common side effect caused by compounds such as Applicants'. This is evidence of the unpredictability in the clinical efficacy of NMDA receptor antagonists such as are present here.

The scope of the claims involves all of the thousands of compounds of claim 1 as well as the hundred of diseases embraced by the term "neurodegenerative conditions". Thus, the scope of claims is very broad.

MPEP §2164.01(a) states, "A conclusion of lack of enablement means that, based on the evidence regarding each of the above factors, the specification, at the time the application was filed, would not have taught one skilled in the art how to make and/or use the full scope of the claimed invention without undue experimentation. *In re Wright*, 999 F.2d 1557,1562, 27 USPQ2d 1510, 1513 (Fed.

Cir. 1993).” That conclusion is clearly justified here and undue experimentation will be required to practice Applicants' invention.

7. Claims 28-31 and 36-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating Alzheimer's disease, does not reasonably provide enablement for preventing any diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. Applicants are not enabled for preventing any of these diseases. The only established prophylactics are vaccines not the fused pyrimidine compounds such as present here. In addition, it is presumed that “prevention” of the claimed diseases would require a method of identifying those individuals who will develop the claimed diseases before they exhibit symptoms. There is no evidence of record that would guide the skilled clinician to identify those who have the potential of becoming afflicted.

The factors to be considered in making an enablement rejection have been summarized above. 1) As discussed above, preventing diseases requires identifying those patients who will acquire the disease before disease occurs. This would require extensive and potentially opened ended clinical research on healthy subjects. 2) The passage spanning lines 1-10, page 9 lists the diseases Applicant

intend to treat. 3) There is no working example of such a preventive procedure in man or animal in the specification. 4) The claims rejected are drawn to clinical medicine and are therefore physiological in nature. 5) The state of the art is that no general procedure is art-recognized for determining which patients generally will become diseased before the fact. 6) The artisan using Applicants invention would be a physician with an MD degree and several years of experience. Despite intensive efforts, pharmaceutical science has been unable to find a way of getting a compound to be effective for the prevention of diseases generally. Under such circumstances, it is proper for the PTO to require evidence that such an unprecedented feat has actually been accomplished, *In re Ferens*, 163 USPQ 609. No such evidence has been presented in this case. The failure of skilled scientists to achieve a goal is substantial evidence that achieving such a goal is beyond the skill of practitioners in that art, *Genentech vs. Novo Nordisk*, 42 USPQ2nd 1001, 1006. This establishes that it is not reasonable to any agent to be able to prevent diseases generally. That is, the skill is so low that no compound effective generally against neurodegenerative disorders has ever been found let alone one that can prevent such conditions. 7) It is well established that "the scope of enablement varies inversely with the degree of unpredictability of the factors involved", and physiological activity is generally considered to be an unpredictable

factor. See *In re Fisher*, 427 F.2d 833, 839, 166 USPQ 18, 24 (CCPA 1970). 8)

The claims broadly read on all patients, not just those undergoing therapy for the claimed diseases and on the multitude of compounds embraced by Formulas IA, IB, or II.

The Examiner suggests deletion of the words "prophylaxis" or "preventing".

8. Claims 36-39 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain and Alzheimer's disease, does not reasonably provide enablement for treating every, "a medical condition or illness affected by modulating nucleoside transport proteins, adenosine kinase, adenosine deaminase, or A1, A2, or A3 receptors". The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection have been summarized above as have the factors leading to this conclusion.

9. Claim 40 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for treating pain, does not reasonably provide enablement for treating any of the other listed diseases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in making an enablement rejection have been summarized above as have the factors leading to this conclusion.

10. Claims 1-7 and 9-40 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for making salts of the claimed compounds, does not reasonably provide enablement for making solvates and hydrates of the claimed compounds. The specification does not enable any person skilled in the art of synthetic organic chemistry to make the invention commensurate in scope with these claims. The factors to be considered in making an enablement rejection] have been summarized above. In the present case the important factors leading to a conclusion of undue experimentation are the absence of any working example of a formed solvate, the lack of predictability in the art, and the broad scope of the claims.

c) There is no working example of any hydrate or solvate formed. The claims are drawn to solvates, yet the numerous examples presented all failed to produce a solvate. These cannot be simply willed into existence. As was stated in *Morton International Inc. v. Cardinal Chemical Co.*, 28 USPQ2d 1190 “The specification purports to teach, with over fifty examples, the preparation of the claimed compounds with the required connectivity. However ... there is no evidence that such compounds exist... the examples of the '881 patent do not

produce the postulated compounds... there is ... no evidence that such compounds even exist.” The same circumstance appears to be true here. There is no evidence that solvates of these compounds actually exist; if they did, they would have formed. Hence, applicants must show that solvates can be made, or limit the claims accordingly.

g) The state of the art is that is not predictable whether solvates will form or what their composition will be. In the language of the physical chemist, a solvate of organic molecule is an interstitial solid solution. This phrase is defined in the second paragraph on page 358 of West (Solid State Chemistry). The solvent molecule is a species introduced into the crystal and no part of the organic host molecule is left out or replaced. In the first paragraph on page 365, West (Solid State Chemistry) says, “it is not usually possible to predict whether solid solutions will form, or if they do form what is their compositional extent”. Thus, in the absence of experimentation one cannot predict if a particular solvent will solvate any particular crystal. One cannot predict the stoichiometry of the formed solvate, i.e. if one, two, or a half a molecule of solvent added per molecule of host. In the same paragraph on page 365 West (Solid State Chemistry) explains that it is possible to make meta-stable non-equilibrium solvates, further clouding what Applicants mean by the word solvate. Compared with polymorphs, there is an

additional degree of freedom to solvates, which means a different solvent or even the moisture of the air that might change the stabile region of the solvate.

h) The breadth of the claims includes all of the hundreds of thousands of compounds of formula IA, IB, and II as well as the presently unknown list of solvents embraced by the term "solvate". Thus, the scope is broad.


Allowable Subject Matter

11. Claim 8 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

12. Information regarding the status of an application should be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at (866) 217-9197 (toll-free). Please direct general inquiries to the receptionist whose telephone number is (703) 308-1235.

13. Please direct any inquiry concerning this communication or earlier communications from the Examiner to Thomas C McKenzie, Ph. D. whose telephone number is (571) 272-0670. The FAX number for amendments is (571) 273-8300. The PTO presently encourages all applicants to communicate by FAX. The Examiner is available from 9:00am to 5:30pm, Monday through Friday. If attempts to reach the Examiner by telephone are unsuccessful, please contact James O. Wilson, acting SPE of Art Unit 1624, at (571)-272-0661.


Thomas C. McKenzie, Ph.D.
Primary Examiner
Art Unit 1624

TCMcK/me